

University of Groningen

Uterine NK cells and macrophages in pregnancy

Faas, Marijke M.; de Vos, Paul

Published in:
Placenta

DOI:
[10.1016/j.placenta.2017.03.001](https://doi.org/10.1016/j.placenta.2017.03.001)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Faas, M. M., & de Vos, P. (2017). Uterine NK cells and macrophages in pregnancy. *Placenta*, 56, 44-52.
<https://doi.org/10.1016/j.placenta.2017.03.001>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



Uterine NK cells and macrophages in pregnancy

Marijke M. Faas^{a, b, *}, Paul de Vos^a

^a Immunoendocrinology, Division of Medical Biology, Department of Pathology and Medical Biology, University of Groningen and University Medical Center Groningen, Groningen, The Netherlands

^b Department of Obstetrics and Gynecology, University of Groningen and University Medical Center Groningen, Groningen, The Netherlands



ARTICLE INFO

Article history:

Received 29 November 2016

Received in revised form

27 February 2017

Accepted 1 March 2017

Keywords:

Uterine NK cells

Macrophages

Decidua

Placental bed

Spiral arteries

ABSTRACT

The presence of immune cells in the placental bed is important for both mother and child. Although various immune cells can be found in the placental bed, such as regulatory T cells and dendritic cells, uterine NK cells and macrophages are the most prominent immune cells in the placental bed in early pregnancy. uNK cell and macrophage numbers in the placental bed decrease in the third trimester. These cells seem to be specifically adapted for their function and environment. uNK cells do not show cytotoxic activity, but are producers of cytokines, growth factors and many other factors. uNK cell function is regulated by inhibitory and activating receptors binding to HLA class I on trophoblast cells. uNK cells are also involved in regulating trophoblast invasion. Macrophages mainly show an M2-like phenotype and also produce cytokines and various other factors. They are important in phagocytosis of various cells and cell debris in the placental bed. Both cell types are also involved in angiogenesis and spiral artery remodeling in the placental bed. In this review we will elaborate on the most important functions of uNK cells and macrophages in the placental bed in humans. We will also discuss animal models, since they may provide clues for function of uNK cells and macrophages in humans.

© 2017 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

During pregnancy, the development of the placenta and the placental bed is important for fetal development. The healthy development of the placental bed not only depends on invasion of fetal trophoblast but also on the presence of immune cells, such as uterine NK cells and macrophages. Since the fetal trophoblast is semi-allogeneic, it seems inevitable that the local immune response at the implantation site has to change in pregnancy. This may be especially important in species with a hemochorial placenta (for instance humans and rodents). The hemochorial placenta is the most invasive type of placenta, in which there is intimate contact between fetal tissue (trophoblast) and the maternal immune system both in the placental bed as well as in the fetal placenta [1]. In this type of placenta, immediately after implantation of the blastocyst, when the endometrium is infiltrated by fetal trophoblasts and transformed into the decidua, the number of immune cells will increase at the implantation site [2]. This is important for proper

regulation of trophoblast invasion and spiral artery remodeling and thus for placentation. This infiltration of immune cells is also important in order to protect the integrity of the uterus and the mother. The immune composition of the decidua is unique [2], since it largely differs from the composition of immune cells in blood and other organs. Most of the leukocytes in the placental bed are innate immune cells, i.e. NK cells and macrophages, which may comprise about 90% of all leukocytes [2,3]. Only about 10% of the immune cells are T cells in early human pregnancy [2,4]. A few dendritic cells, granulocytes and B cells can be found [2,5]. Since uterine NK cells and macrophages are the most prominent cells in the placental bed, the present review will focus on the roles of these cells at the maternal fetal interface. We will mainly focus on humans, but we will discuss rodent models since these animals are often used as models for the human placental bed.

2. Human fetal maternal interface

The placenta is important in maternal-fetal exchange of nutrients and gases. In a hemochorial placenta, this is possible through fetal villous tissue bathing in maternal blood [6]. To accomplish the maternal blood circulation in the placenta, during placentation, several changes have to take place in the uterus. First, the

* Corresponding author. Immunoendocrinology, Division of Medical Biology, Department of Pathology and Medical Biology, University Medical Center Groningen, Hanzplein 1, 9713 GZ, Groningen, The Netherlands.

E-mail address: m.m.faas@umcg.nl (M.M. Faas).

endometrium at the site of implantation differentiates into the decidua basalis. Then placental villous trophoblasts, differentiate into extravillous trophoblasts, which consists of 2 populations: interstitial and extravascular trophoblast. First interstitial trophoblasts invade into the decidua. Then, endovascular trophoblasts invade into the decidua as well as into the inner third of the myometrium and extensively remodel the uterine spiral arteries. During this process the endovascular trophoblasts become embedded intramurally in the fibrinoid layer, which replaces the original vascular smooth muscles [7]. Finally, reendothelialization occurs [7]. At the end of this process, the spiral arteries are remodeled into large diameter conduit vessels with low resistance assuring a constant blood supply to the intervillous space of the placenta [7]. The placental bed, consisting of both decidua and myometrial segments, and containing the (remodeled) spiral arteries, is thus important for blood supply into the intervillous space [7]. The remodeling of the spiral arteries is accomplished by the presence of both fetal trophoblast cells and maternal immune cells [7] (see also Fig. 1, showing the placental bed at the time of trophoblast invasion and spiral artery remodeling, 16–20 weeks of pregnancy).

3. Rodent fetal maternal interface

Like humans, rodents also have a hemochorial placenta. Maternal-fetal exchange takes place in the labyrinth. Rodents are often used as animal models to study pregnancy and pregnancy related problems. Unique to the rodent placental bed is the development of the mesometrial triangle [8]. This structure develops on the mesometrial side of the rodent uterus at about midgestation. In this structure, decidualized cells as well as many

immune cells, mainly uNK cells and macrophages, are present. This structure also contains spiral arteries. The spiral arteries traverse the decidua basalis and then converge to form 1–4 centrally located arterial channels [8]. The channels then traverse the labyrinth and maternal blood flow into the labyrinth is from the embryonic site [8]. The mesometrial triangle is considered as the rodent equivalent of the deeper part of the human placental bed. Although the mesometrial triangle is present in both rats and mice, trophoblast invasion into this triangle is different between these species. In rats, deep trophoblast invasion into the mesometrial triangle is found until the myometrium [9], while in mice trophoblast invasion beyond the decidua is not found [8]. However, in both rats and mice, spiral artery remodeling in the mesometrial triangle is found [8,9] (see also Fig. 1). Many studies on mice have been done on spiral artery remodeling in the decidua, since in this part of the mouse placental bed both trophoblast and immune cells are present. The mesometrial triangle in the rat is often used as a model for deep spiral artery remodeling in humans, since in rats in the mesometrial triangle both trophoblast and immune cells are present.

4. Immune cells in the decidua in human pregnancy

The placental bed contains many immune cells during pregnancy. Immunohistochemical studies have shown that during early pregnancy 30–40% of all cells in the decidua are leukocytes [10]. Leukocytes are, however, present in the placental bed during all stages of pregnancy [3,11]. These leukocytes consist of uNK cells, macrophages and also T lymphocytes [3,10,11]. Most T lymphocytes present during pregnancy are CD8 cytotoxic T lymphocytes [3,10], although Kwan et al. found that only about 50% of T lymphocytes

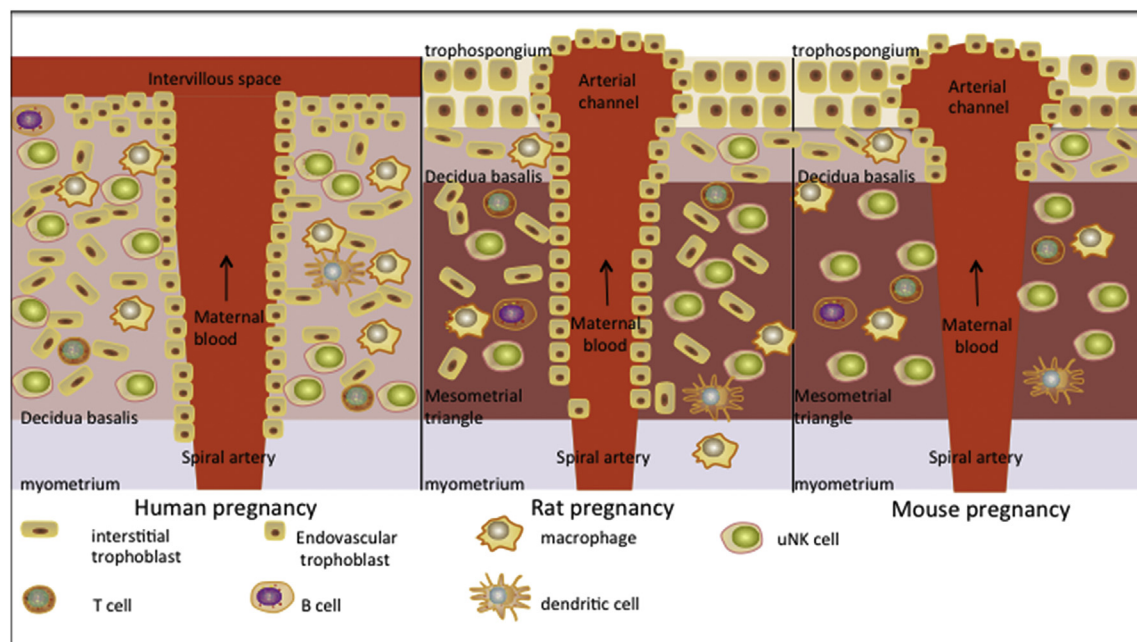


Fig. 1. Placental bed with spiral arteries and immune cells in humans (between weeks 16–20) and rodents (around day 18). The placental bed of humans consists of the decidua basalis and the inner part of the myometrium, which are both invaded by trophoblast and immune cells. The remodeled spiral arteries, which are, at this time of pregnancy (i.e. between week 16 and 20) aligned with trophoblast until the myometrium, supply blood into the intervillous space. Note that re-endothelialization takes place in the third trimester and is therefore not seen in this figure.

The rodent placental bed consists of the decidua basalis and the mesometrial triangle, the equivalent of the deeper part of the placental bed in humans. Remodeled spiral arteries supply blood into the arterial channel (or channels), which then traverse the labyrinth and maternal blood flows into the labyrinth from the fetal side. In rodents, immune cells can be found throughout the decidua and mesometrial triangle. In the rat, trophoblasts invade into the decidua and mesometrial triangle and are important for spiral artery remodeling and trophoblast invasion. In the mouse, extravillous trophoblasts only invade into the decidua, not into the mesometrial triangle. Spiral artery remodeling in the mesometrial triangle is therefore dependent on the immune cells. Note that re-endothelialization takes place later in pregnancy and is not seen yet.

were CD8 positive [11]. The numbers of these cells may slightly increase towards the third trimester of pregnancy [3,11]. Most prominent leukocyte populations in the placental bed seem to be the uNK cells [3,10,12], and the macrophages [3,10]. Higher numbers of these cell populations are found in the placental bed during the first and second trimester as compared with the third trimester [3,11].

4.1. Uterine NK cells

NK cells were originally described as lymphocytes with natural cytotoxicity against tumor cells [13]. It has, however, since long been established that NK cells are a lymphocyte population, separate from T and B cells, with cytotoxic and cytokine producing effector functions [13]. In humans, they are recognized by CD56 expression and lack of expression of CD3 [14]. Two populations of circulating NK cells can be distinguished in humans, i.e. the cytotoxic NK cells, which are CD56dim/CD16+ and represent about 90% of all circulating NK cells in humans and the cytokine producing NK cells, which are CD56++/CD16- [13]. They are suggested to be a regulatory subset.

Uterine NK cells (uNK) cells in the human endometrium and placental bed are CD56++/CD16-. They, however, are different from the CD56++/CD16- NK cell population in the blood, since they are highly granulated, while peripheral blood CD56++/CD16- NK cells are not granulated. They also express different markers as compared to blood NK cells [2]. uNK cells are already present in the endometrium at the menstrual cycle: they are present in small numbers in the proliferative and early secretory phase endometrium, while numbers increase in the late secretory phase of the menstrual cycle [4,10]. The numbers of uNK cells increase during early pregnancy and they are the dominating population in the first trimester decidua (about 70% of all leukocytes) [4,10]. Although some studies have shown that uNK cells decrease dramatically in number after the first trimester and are nearly absent in the second and third trimester [12], other studies, however, do suggest that they are present during all stages of pregnancy [3,15]. uNK cells are usually found in the vicinity of invading fetal trophoblast cells [16], and in the vicinity of spiral arteries being remodeled [17].

4.1.1. Function of uNK cells

The exact *in vivo* function of uterine NK cells is not clear yet. However, their location suggest that they are involved in trophoblast invasion and spiral artery remodeling. *In vitro* studies have been performed to evaluate the effect of uNK cells on trophoblast invasion. These *in vitro* data showed inconsistent results, since studies showed that *in vitro* uNK cells increased [18,19], decreased [20] or not affected [19] trophoblast invasion. These inconsistencies between the studies may be due to the time of pregnancy at which the uNK were isolated, since uNK isolated from week 8–10 did not affect trophoblast invasion, while uNK cells isolated from days 12–14 did increase trophoblast invasion *in vitro* [19]. Also differences in methods between the studies may have affected the results, since isolated trophoblast are used [18], but also villous explants [19,20] to study trophoblast invasion.

Knowledge on human uNK cell function is mainly derived from studies performed using isolated uNK from early pregnancy decidual tissue, retrieved after elective abortion. Unfortunately, placental bed is lacking in this material and it is not feasible to get material from other gestational ages, apart from after delivery. It has been shown since long that in early pregnancy uNK cells do exhibit cytotoxic activity against an NK cell target K562 [21]. This cytotoxicity is, however, lower than that of peripheral NK cells [21]. uNK cells do not show cytotoxicity against extravillous trophoblast cells [22]. It is thought that the main function of uNK cells is to

produce cytokines, growth factors, angiogenic factors and other factors. Indeed, already in the 1990's it was shown that uNK cells produce a variety of cytokines, such as Tumor necrosis factor α (TNF α), interleukin-10, interleukin-1 β , Transforming growth factor β (TGF β) and interferon γ (IFN γ) [23] as well as Macrophage-Colony stimulating factor (M-CSF) or Granulocyte macrophage-colony stimulating factor (GM-CSF) [18]. In later studies it was shown that uNK cells also produce angiogenic growth factors, such as vascular endothelial growth factor-C (VEGF-C), Placental growth factor (PIGF) and angiopoietin-1 [24,25] and proteases, such as metalloproteinases (MMPs) [26].

uNK cell function seems to be regulated by their expression of NK cell receptors, such as NKG2A, LILRB1 and receptors of the KIR family [27]. These receptors bind to unique forms of HLA class I, HLA-C, E and G, expressed by extravillous trophoblast (EVT) [28]. The communication between EVT expressing HLA and KIR expressing uNK has been evaluated in various studies. For instance, growth factor production by uNK cells seems to depend on direct contact between uNK cells and trophoblast, suggesting that receptor-ligand interactions are needed [29]. The polymorphic killer cell immunoglobulin-like receptors (KIRs) seem to be important in balancing the NK activating and inhibitory signaling [30], since it has been shown that binding of KIR2D with HLA-C modulates uNK responses and may alter trophoblast migration and spiral artery remodeling [27]. Specific combinations of these receptor-ligand bindings are important for healthy pregnancy, since genetic association studies have suggested that allel-recognition of fetal HLA-C2 of the KIR B haplotype might be important for normal placental development. On the other hand, allel-recognition of HLA-C2 of the maternal KIR AA genotype increased the risk for preeclampsia in various ethnic populations [31].

In spiral artery remodeling two different steps can be identified. The first step is the loss of the musculo-elastic structure and the formation of endothelial cell layer breaks [32]. This first process takes place in the absence of trophoblast cells, but in the presences of uNK cells and macrophages, suggesting an important role for these immune cells in this first step of spiral artery remodeling [17,33,34]. In the second step, fetal trophoblasts, especially endothelial trophoblast, are attracted towards the arteries, transiently replacing the endothelial lining in the decidua and partly in the myometrium. At this time, also many uNK cells are still found in the vicinity of the spiral arteries, suggesting a role for these cells at this second step as well [17].

4.1.2. Origin of uNK cells

The origin of uNK cells and the reason for their increase at the fetal maternal interface during pregnancy is not well established. However, several mechanisms have been proposed. The first mechanism is the recruitment of peripheral blood NK cells, i.e. the CD56++/CD16- cells that differentiate locally into uNK cells [35,36]. This suggestion is supported by the fact that decidual cells and trophoblasts secrete large amounts of NK cell chemoattractants, such as IP-10, MCP-1 [35]. The second suggestion is that uNK cells mature from endometrial NK cells in response to pregnancy-associated factors, such as hormones (progesterone) or IL-15 [37]. Another suggestion is that uNK cells differentiate from hematopoietic precursors present in the decidua in response to decidual stromal factors [35,38]. These three mechanisms could also act in parallel.

4.1.3. uNK cells in rodent models

Much of the knowledge on the role of uNK cells in the development of the placental bed arises from mouse studies. Although in mice uNK cells only appear in the decidua basalis by day 6.5, and

not immediately after implantation as in humans, similar to human uNK cells, murine uNK cells are activated [39], express interferon gamma [40] and the mouse equivalent of KIR receptor, LY49 [41]. They also express growth factors, such as VEGF A and placental growth factor [42,43]. Many studies in mice have shown an important role of uNK cells in spiral artery remodeling in the decidua, which in the mouse, decidual spiral artery remodeling occurs between day 8.5 and day 10.5 of pregnancy (mouse pregnancy lasts for 19–20 days) [40]. uNK cells play a major role in this spiral artery remodeling, since NK cell deficient mice lack spiral artery remodeling and have abnormal decidual and myometrial structures at midgestation [44,45]. Indeed, after reconstitution of NK cells in NK cell deficient mice, spiral artery remodeling was normal [46]. It seems to be especially IFN γ production by uNK cells, that is important for the spiral artery remodeling, since systemic administration of IFN γ to NK cell deficient mice also resulted in normal spiral artery remodeling [40,47,48]. Interestingly, mouse uNK cells do not limit trophoblast invasion into the decidua [46].

Spiral artery remodeling has also been shown in rats [9,49]. In contrast to the mouse, deep trophoblast invasion in the rat into the mesometrial triangle, up to the myometrium has been found [9,50], which makes the rat a good model for spiral artery remodeling in the deeper parts of the placental bed in humans. The role for uNK cells in spiral artery remodeling and trophoblast invasion has been less well characterized in rats as compared with mice. However, in contrast to mice, in rats uNK cells seem to interfere with trophoblast invasion, especially in the mesometrial triangle. This is for instance apparent from the locations of uNK cells vs interstitial trophoblast. Staining of uNK cells and trophoblast in consecutive sections of the mesometrial triangle on days 15, 17 and 20 of rat pregnancy shows that trophoblast invasion seemed to follow the demise of uNK cells in the direction of the myometrium (see also Fig. 2). This suggests that uNK cells regulate interstitial trophoblast invasion. They also seem to regulate intravascular trophoblast invasion, since depletion of NK cells in early pregnancy, resulted in

increased endovascular trophoblast invasion at day 13 [51]. Unfortunately, no studies with NK cell depletion have been done in pregnant rats beyond day 13 in order to study the effect of uNK on interstitial trophoblast invasion in healthy pregnant rats.

A role for uNK cells in spiral artery development and remodeling has been shown by Chakraborty et al. [51]. These authors have shown that uNK cells promote uterine spiral artery growth towards the ectoplacental cone [51] and that uNK cells cause a partial disruption of the spiral artery tunica media integrity [51]. Data from our lab also indicated a role for uNK cells in spiral artery remodeling, since we found partly remodeled spiral arteries in the mesometrial triangle of day 15 of pregnancy in the presence of uNK cells, but without the presence of interstitial trophoblast (see Fig. 3). However, apparently, for complete spiral artery remodeling in the mesometrial triangle in the rat, endovascular trophoblast invasion is needed [51,52].

4.2. Uterine macrophages

Macrophages can be found in all tissues and they are important in the detection, ingestion and processing of foreign material, dead cells and other debris [53]. They are derived from monocytes [53], which are recruited into tissues to replenish steady state macrophages or they are recruited to inflammatory tissue [53]. Macrophages do not only play a role in inflammation, they also have an important role in the resolution of inflammation [53]. Several subsets of macrophages have now been described. Some years ago, they were subdivided into 2 groups: M1 (classically activated macrophages) and M2 (alternatively activated macrophages) [54]. M1 macrophages are microbicidal and inflammatory, while M2 macrophages are immunomodulatory, inducing tolerance and resolution of inflammation [54]. However, more recently it was found that these 2 populations are extreme ends of polarization and many different intermediate types of macrophages can be found [55].

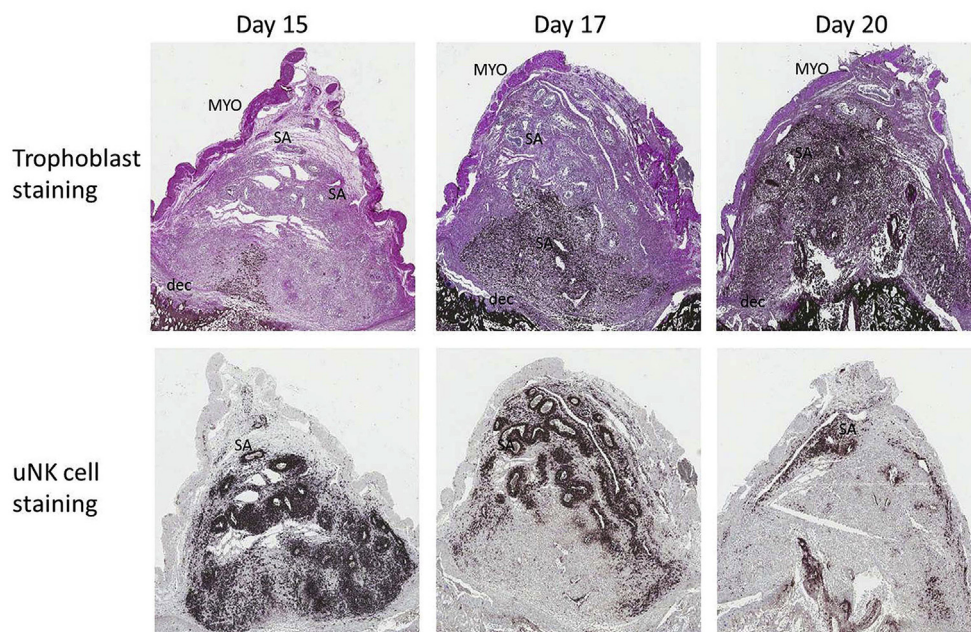


Fig. 2. Mesometrial triangle of 15, 17 and 20 days pregnant rats, stained for trophoblasts (black staining; top row) or NK cells (black staining, lower row) (all sections were stained according to protocols described by Spaans et al. [9]). At day 15, little interstitial trophoblast invasion is observed in the mesometrial triangle, while NK cells are prominent throughout the whole mesometrial triangle, mainly found in a cuff around the spiral arteries (SA). At day 17, interstitial trophoblasts have further invaded into the mesometrial triangle towards the myometrium (MYO), while uNK cells have retracted into the direction of the myometrium. At day 20, there is a further demise of the uNK cells, which is associated with even further invasion of the interstitial trophoblast into the mesometrial triangle until the myometrium. (dec = decidua).

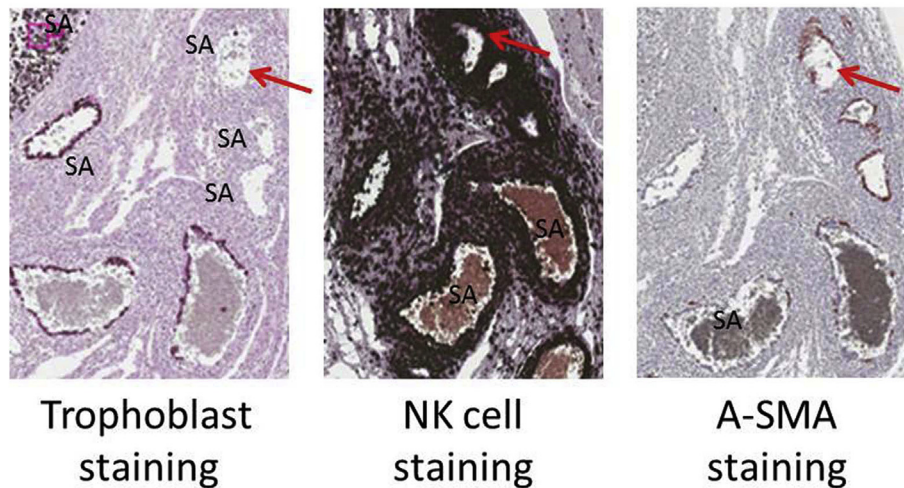


Fig. 3. Spiral arteries (SA) in the mesometrial triangle of day 15 pregnant rats stained for trophoblast (left photograph), uNK cells (middle photograph) and α -smooth muscle actin (SMA) (right photograph). (sections are stained according to protocols described by Spaans et al. [9]). It can be seen that trophoblast staining is absent in the spiral artery at the top right of the left photograph (red arrow), while the same spiral artery in the middle photograph shows an abundant uNK cells cuff. The right photograph shows that despite the absence of trophoblasts, but in the presence of uNK cells, the smooth muscle cells have partly disappeared, indicating spiral artery remodeling.

Low numbers of macrophages can already be found in the endometrium of non-pregnant women, although they fluctuate during the menstrual cycle [10]. It seems therefore likely that these cells are under hormonal control [56]. After fertilization, the number of uterine macrophages immediately increases [57], so that 20–30% of all decidual leukocytes are macrophages in early pregnancy [58]. Although macrophages are present in the placental bed at all times during pregnancy [59], the number of decidual macrophages vary with gestational age with the highest numbers found in the first and second trimester [60].

4.2.1. Macrophage function

Various studies have focused on specific functions of macrophages in the human placental bed and these cells seem to have various roles during pregnancy. They play a role in spiral artery remodeling and trophoblast invasion [59,61], but they may also play a role in blastocyst implantation [62] and in protecting the fetus against intrauterine infection [63]. The putative role of macrophages in spiral artery remodeling is shown by their presence around spiral arteries in the human placental bed. They can specifically be found in the vicinity of spiral arteries that show disruption and disorganization of vascular smooth muscle cells and endothelial cells, while no extravillous trophoblast was present at that time [17]. This suggests that macrophages prepare spiral arteries for further remodeling by trophoblast cells. In accordance with this role, decidual macrophages produce many factors associated with angiogenesis and tissue remodeling [64,65]. During spiral artery remodeling by trophoblast, apoptotic trophoblast cells can be found [66]. One of the roles of the macrophages present around spiral arteries at that time may be to engulf these apoptotic cells, thereby preventing the release of proinflammatory substances into the decidua [67].

Since placental bed macrophages express various M2 markers, such as CD206, CD163 and DC-sign, they seem to be M2-like macrophages, i.e. immunomodulatory macrophages [68,69]. They may, however, not be the typical M2 macrophages, since they are not induced by Th2 cytokines, but by M-CSF and IL-10 in *in vitro* studies [70]. One study suggested the presence of two macrophage subpopulations in the early decidua (6–12 weeks of pregnancy): a more proinflammatory and a more regulatory subset, which was

higher in number as compared with the proinflammatory subset [71].

As indicated above, also at the end of pregnancy, macrophages can be found in the placental bed. Although it is recognized that these macrophages are of the M2 phenotype [72], the exact role of these decidual macrophages at the end of pregnancy remains to be established. It seems likely, however, that similar to early pregnancy, also in late pregnancy they are involved in clearance of apoptotic cells and immunoregulation.

4.2.2. Origin of decidual macrophages

Although it has always been thought that monocytes are the sole precursors of tissue macrophages, for many tissues, such as liver, lung, brain, it has now been shown that macrophages arise from macrophage progenitors from the yolk sac [73–75]. These precursors migrate to the various tissue during embryonic life and are maintained in these tissues during adult life [75]. Mucosal tissues, such as the decidua, seem to be an exception, since macrophages in these tissues appear to be mainly derived from blood monocytes [74]. Monocytes are short-lived circulating cells, comprising about 5–10% of the circulating blood leukocytes [53]. In humans, three monocyte subsets are found, which differ in many aspects [53]. Classical monocytes, representing 90–95% of all monocytes, arise from the bone marrow and mature in the circulation via intermediate monocytes into non-classical monocytes [76], the other 2 monocyte subsets. Classical monocytes are phagocytes and generate reactive oxygen species and produce cytokines, while non classical monocytes are only weak phagocytes, but more efficient producers of pro-inflammatory cytokines [53]. Non-classical monocytes patrol the endothelium to survey for endothelial cell damage and infection [53]. Non-classical monocytes have been shown to be increased in various inflammatory diseases [53] and also in pregnancy [77,78]. In rodents, also classical and non-classical monocytes have been described [77,79]. The functions of the subtypes appear similar between humans and rodents.

It is unknown whether macrophages in the placental bed arise from classical or non-classical monocytes during pregnancy. Tagliani et al. have shown that in mice mainly classical monocytes and not non-classical monocytes, infiltrate into the decidua in early

pregnancy [80]. This suggests that the decreased number of classical monocytes during pregnancy is due to an increased infiltration of these monocytes into the decidua. Recently, it has also been suggested that classical monocytes preferentially differentiate into M1 macrophages, and non-classical monocytes preferentially differentiate into M2 macrophages [81]. Since macrophages in the placental bed are mainly of the M2-like type, this suggests that non-classical monocytes would preferentially invade into the decidua. Further studies are therefore needed to evaluate the role of the different monocyte subsets in populating the macrophages in the placental bed.

4.2.3. Decidual macrophages in rodent models

Since it is difficult to study the role of macrophages in the placental bed in humans, the use of animal models help in understanding the function of macrophages in the decidua. In mice, macrophages are present in the decidua and myometrium [82]. In early pregnancy in mice they are found scattered throughout the decidua [83]. At the end of pregnancy, macrophages are the largest population of immune cells in the mouse decidua [84]. Not much is known about the function of these cells in the mouse placental bed.

In the rat, we and others found many macrophages in the mesometrial triangle [9,85]. They were found throughout the interstitium but also around the spiral arteries, but with no apparent relation with the state of the remodeling of the arteries. Only a few M2 macrophages were found in the mesometrial triangle of healthy pregnant rats at the end of pregnancy [9]. These results indicate that in the rat, macrophages may not have a prominent role in spiral artery remodeling in the mesometrial triangle. It could indicate that they are important for phagocytosis of apoptotic cells and debris released during the spiral artery remodeling. Further studies into these placental bed cells are necessary and help in defining the role of placental bed macrophages in humans.

5. NK cells and macrophages in cancer

Being part of a special edition of *Placenta* following the Lumps and Bumps Conference 2016, this last paragraph will focus on the similarities and differences between immune cells in the decidua and in tumors. Trophoblast cells are often compared with tumor cells, since they invade the decidual tissue, like tumor cells invade normal tissue [86]. As described above, the decidua contains a lot of immune cells, mainly uNK and macrophages. Also tumors are infiltrated by immune cells, mostly T cells [87], but also NK cells and macrophages [88,89].

In contrast to the placental bed, tumors contain only a low number of NK cells, which suggests that NK cells do not efficiently home to tumor tissue [90]. As in the decidua, in some tumors it has been shown that the cytokine producing NK cells subset (CD56++CD16- NK cells) are enriched in the tumor [91,92]. This indicates that these NK cells mainly produce cytokines, and do not exert direct tumor cell killing. Indeed, the NK cells present in a tumor may have a distinct phenotype: depending on the cancer type, they may express increased numbers of inhibitory receptors [93] or decreased numbers of activating receptors [92]. Communication between tumor cells and NK cells seem to be important for regulating NK cells function. For instance, the NK cell activating receptor, DNAM-1, seems to be downregulated by ovarian carcinoma cells [92]. Another example of tumor cells regulating NK cell function is the induction of the production of regulatory cytokines and diminished granule mobilization, cytotoxicity and IFN γ production by NK cells after binding to CD137 on acute myeloid leukemia cells. These data suggest that tumors do not promote infiltration of NK cells and if NK cells do infiltrate, tumor cells down

regulate their tumor killing activity [94]. This is partly similar to the situation in the decidua: although the decidua promotes infiltration of NK cells, trophoblasts present in the decidua do regulate uNK cell function to make sure they do not kill trophoblast cells.

Macrophages are another important cell type in the tumor environment. They are usually referred to as tumor associated macrophages (TAM) and are the most abundant immune cells in solid tumors [95]. Their presence correlates with worse disease prognosis and higher frequency of metastasis in various cancers [96–98]. As in the placental bed, in tumors, most macrophages are derived from circulating monocytes, and thus from hematopoietic precursors [89,99]. The role of TAMs in the tumor may vary, depending on the tumor type. In colorectal tumors, for instance, TAMs are proinflammatory and play an antitumor role [100,101]. The antitumor effect may be due to the production of various proinflammatory cytokines by the TAMs, which activate cytotoxic T cells, and induce an antitumor immune response [100]. However, in most tumor types, such as breast cancer, ovarian cancer, cervical cancer and lung cancer, TAMs show an M2-like phenotype, expressing M2 markers, like CD163 or C-type lectin domains [102,103]. The M2-like phenotype is induced and maintained by other immune cells in the tumor (such as T cells) as well as by tumor cells [104,105]. The M2 TAMs in tumors promote angiogenesis [96], lymphangiogenesis [106] tumor growth [107–109]. Thus TAMs, like decidual macrophages, are mainly recruited from monocytes, are mainly of the M2-like phenotype and are angiogenic and immunoregulatory. Similar to decidual macrophages, which promote placental growth and development, TAMs promote tumor growth and development.

6. Conclusion

Although in the past, it was thought that uNK cells and macrophages in the placental bed were dangerous for pregnancy, it is now known that these cells are very important for implantation and normal development of the placental bed and thus the placenta. Both cell types are found in the vicinity of EVT and spiral arteries, suggesting that they have a role in trophoblast invasion and spiral artery remodeling. uNK cell function may depend on the presence of extravillous trophoblast, which express specific HLA class I molecules, which bind to inhibitory and activating receptors on uNK cells. The exact mechanisms by which these cells affect the vascular wall remain to be established. Both cell types aid in spiral artery remodeling by producing cytokines, growth factors and other factors. Macrophages, may also help in spiral artery remodeling by clearance of apoptotic cells and cell debris. Both cell types also have other functions in the decidua, such as angiogenesis and immunoregulation (see Fig. 4).

Animal studies are useful in understating the role of uNK cells and macrophages in pregnancy complications, since uNK cells and macrophages may play similar roles in the placental bed of rodents as compared with humans. Such studies into the roles of uNK cells in physiological and pathological development of the placental bed may in the future result in (immune) therapies for pregnancy complications.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

We have no conflict of interest.

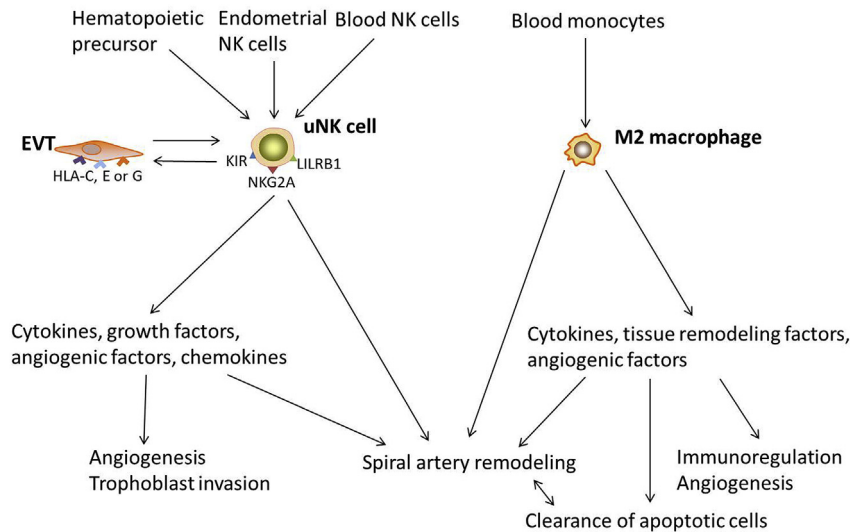


Fig. 4. The role of uNK cells and macrophages in the development of the placental bed. uNK cells and macrophages are both involved in spiral artery remodeling and production of cytokines and other factors in the placental bed. uNK cell function may depend on the binding inhibitory and activating receptors of these cells HLA on EVT. Both cell types may directly affect the vascular wall, although they may also indirectly affect the vascular wall by the production of cytokines and other factors. Macrophages may also aid in spiral artery remodeling by clearance of apoptotic cells and cell debris and producing various tissue remodeling factors. Both cell types also have other functions in the decidua, such as angiogenesis and immunoregulation.

References

- [1] E.N.T. Meeusen, R.J. Bischof, C.S. Lee, Comparative T-cell responses during pregnancy in large animals and humans, *Am. J. Reprod. Immunol.* 46 (2001) 169–179.
- [2] A. Trundley, A. Moffett, Human uterine leukocytes and pregnancy, *Tissue Antigens* 63 (1) (2004) 1–12.
- [3] P.J. Williams, R.F. Searle, S.C. Robson, B.A. Innes, J.N. Bulmer, Decidual leukocyte populations in early to late gestation normal human pregnancy, *J. Reprod. Immunol.* 82 (1) (2009) 24–31.
- [4] A. King, V. Wellings, L. Gardner, Y.W. Loke, Immunocytochemical characterization of the unusual large granular lymphocytes in human endometrium throughout the menstrual cycle, *Hum. Immunol.* 24 (1989) 195–205.
- [5] J.N. Bulmer, P.M. Johnson, Macrophage populations in the human placenta and amniochorion, *Clin. Exp. Immunol.* 57 (2) (1984) 393–403.
- [6] H.W. Boyd JD, *The Human Placenta*, Heffer and Sons, Cambridge, 2013.
- [7] R. Pijnenborg, L. Vercruyse, M. Hanssens, The uterine spiral arteries in human pregnancy: facts and controversies, *Placenta* 27 (9–10) (2006) 939–958.
- [8] S.L. Adamson, Y. Lu, K.J. Whiteley, D. Holmyard, M. Hemberger, C. Pfarrer, J.C. Cross, Interactions between trophoblast cells and the maternal and fetal circulation in the mouse placenta, *Dev. Biol.* 250 (2) (2002) 358–373.
- [9] F. Spaans, B.N. Melgert, C. Chiang, T. Borghuis, P.A. Klok, P. de Vos, H. van Goor, W.W. Bakker, M.M. Faas, Extracellular ATP decreases trophoblast invasion, spiral artery remodeling and immune cells in the mesometrial triangle in pregnant rats, *Placenta* 35 (8) (2014) 587–595.
- [10] J.N. Bulmer, L. Morrison, M. Longfellow, A. Ritson, D. Pace, Granulated lymphocytes in human endometrium: histochemical and immunohistochemical studies, *Hum. Reprod.* 6 (6) (1991) 791–798.
- [11] M. Kwan, A. Hazan, J. Zhang, R.L. Jones, L.K. Harris, W. Whittle, S. Keating, C.E. Dunk, S.J. Lye, Dynamic changes in maternal decidual leukocyte populations from first to second trimester gestation, *Placenta* 35 (12) (2014) 1027–1034.
- [12] A. Moffett-King, Natural killer cells and pregnancy, *Nature reviews, Immunology* 2 (9) (2002) 656–663.
- [13] E. Vivier, E. Tomasello, M. Baratin, T. Walzer, S. Ugolini, Functions of natural killer cells, *Nat. Immunol.* 9 (5) (2008) 503–510.
- [14] M.J. Robertson, J. Ritz, Biology and clinical relevance of human natural killer cells, *Blood* 76 (12) (1990) 2421–2438.
- [15] L. Rieger, S. Segerer, T. Bernar, M. Kapp, M. Majic, A.K. Morr, J. Dietl, U. Kammerer, Specific subsets of immune cells in human decidua differ between normal pregnancy and preeclampsia—a prospective observational study, *Reproductive Biol. Endocrinol. RB&E* 7 (2009) 132.
- [16] C. Helige, H. Ahammer, G. Moser, A. Hammer, G. Dohr, B. Huppertz, P. Sedlmayr, Distribution of decidual natural killer cells and macrophages in the neighbourhood of the trophoblast invasion front: a quantitative evaluation, *Hum. Reprod.* 29 (1) (2014) 8–17.
- [17] S.D. Smith, C.E. Dunk, J.D. Aplin, L.K. Harris, R.L. Jones, Evidence for immune cell involvement in decidual spiral arteriole remodeling in early human pregnancy, *Am. J. pathology* 174 (5) (2009) 1959–1971.
- [18] J. Hanna, D. Goldman-Wohl, Y. Hamani, I. Avraham, C. Greenfield, S. Natanson-Yaron, D. Prus, L. Cohen-Daniel, T.I. Arnon, I. Manaster, R. Gazit, V. Yutkin, D. Benharroch, A. Porgador, E. Keshet, S. Yagel, O. Mandelboim, Decidual NK cells regulate key developmental processes at the human fetal-maternal interface, *Nat. Med.* 12 (9) (2006) 1065–1074.
- [19] G.E. Lash, H.A. Otun, B.A. Innes, K. Percival, R.F. Searle, S.C. Robson, J.N. Bulmer, Regulation of extravillous trophoblast invasion by uterine natural killer cells is dependent on gestational age, *Hum. Reprod.* 25 (5) (2010) 1137–1145.
- [20] Y. Hu, J.P. Dutz, C.D. MacCalman, P. Yong, R. Tan, P. von Dadelszen, Decidual NK cells alter in vitro first trimester extravillous cytotrophoblast migration: a role for IFN-gamma, *J. Immunol.* 177 (12) (2006) 8522–8530.
- [21] A. Ritson, J.N. Bulmer, Isolation and functional studies of granulated lymphocytes in first trimester human decidua, *Clin. Exp. Immunol.* 77 (2) (1989) 263–268.
- [22] L.J. Chen, Z.Q. Han, H. Zhou, L. Zou, P. Zou, Inhibition of HLA-G expression via RNAi abolishes resistance of extravillous trophoblast cell line TEV-1 to NK lysis, *Placenta* 31 (6) (2010) 519–527.
- [23] S. Saito, K. Nishikawa, T. Morii, M. Enomoto, N. Narita, K. Motoyoshi, M. Ichijo, Cytokine production by CD16-CD56bright natural killer cells in the human early pregnancy decidua, *Int. Immunol.* 5 (5) (1993) 559–563.
- [24] G.E. Lash, B. Schiessl, M. Kirkley, B.A. Innes, A. Cooper, R.F. Searle, S.C. Robson, J.N. Bulmer, Expression of angiogenic growth factors by uterine natural killer cells during early pregnancy, *J. Leukoc. Biol.* 80 (3) (2006) 572–580.
- [25] P.P. Jokhi, A. King, Y.W. Loke, Production of granulocyte-macrophage colony-stimulating factor by human trophoblast cells and by decidual large granular lymphocytes, *Hum. Reprod.* 9 (9) (1994) 1660–1669.
- [26] K. Naruse, G.E. Lash, B.A. Innes, H.A. Otun, R.F. Searle, S.C. Robson, J.N. Bulmer, Localization of matrix metalloproteinase (MMP)-2, MMP-9 and tissue inhibitors for MMPs (TIMPs) in uterine natural killer cells in early human pregnancy, *Hum. Reprod.* 24 (3) (2009) 553–561.
- [27] S. Xiong, A.M. Sharkey, P.R. Kennedy, L. Gardner, L.E. Farrell, O. Chazara, J. Bauer, S.E. Hiby, F. Colucci, A. Moffett, Maternal uterine NK cell-activating receptor KIR2DS1 enhances placentation, *J. Clin. Invest.* 123 (10) (2013) 4264–4272.
- [28] A. King, S.E. Hiby, L. Gardner, S. Joseph, J.M. Bowen, S. Verma, T.D. Burrows, Y.W. Loke, Recognition of trophoblast HLA class I molecules by decidual NK cell receptors—a review, *Placenta* 21 (Suppl A) (2000) S81–S85.
- [29] G.E. Lash, K. Naruse, A. Robson, B.A. Innes, R.F. Searle, S.C. Robson, J.N. Bulmer, Interaction between uterine natural killer cells and extravillous trophoblast cells: effect on cytokine and angiogenic growth factor production, *Hum. Reprod.* 26 (9) (2011) 2289–2295.
- [30] A. Thielens, E. Vivier, F. Romagne, NK cell MHC class I specific receptors (KIR): from biology to clinical intervention, *Curr. Opin. Immunol.* 24 (2) (2012) 239–245.
- [31] S.E. Hiby, J.J. Walker, K.M. O'Shaughnessy, C.W. Redman, M. Carrington, J. Trowsdale, A. Moffett, Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success, *J. Exp. Med.* 200 (8) (2004) 957–965.
- [32] L.K. Harris, Review: trophoblast-vascular cell interactions in early pregnancy: how to remodel a vessel, *Placenta* 31 (Suppl) (2010) S93–S98.

- [33] A. Robson, L.K. Harris, B.A. Innes, G.E. Lash, M.M. Aljunaidy, J.D. Aplin, P.N. Baker, S.C. Robson, J.N. Bulmer, Uterine natural killer cells initiate spiral artery remodeling in human pregnancy, *FASEB J.* 26 (12) (2012) 4876–4885.
- [34] C.M. Craven, T. Morgan, K. Ward, Decidual spiral artery remodelling begins before cellular interaction with cytotrophoblasts, *Placenta* 19 (4) (1998) 241–252.
- [35] C. Carlinio, H. Stabile, S. Morrone, R. Bulla, A. Soriani, C. Agostinis, F. Bossi, C. Mocchi, F. Sarazani, F. Tedesco, A. Santoni, A. Gismondi, Recruitment of circulating NK cells through decidual tissues: a possible mechanism controlling NK cell accumulation in the uterus during early pregnancy, *Blood* 111 (6) (2008) 3108–3115.
- [36] D.B. Keskin, D.S. Allan, B. Rybalov, M.M. Andzelm, J.N. Stern, H.D. Kopcow, L.A. Koopman, J.L. Strominger, TGFbeta promotes conversion of CD16+ peripheral blood NK cells into CD16- NK cells with similarities to decidual NK cells, *Proc. Natl. Acad. Sci. U. S. A.* 104 (9) (2007) 3378–3383.
- [37] I. Manaster, S. Mizrahi, D. Goldman-Wohl, H.Y. Sela, N. Stern-Ginossar, D. Lankry, R. Gruda, A. Hurwitz, Y. Bdolah, R. Haimov-Kochman, S. Yagel, O. Mandelboim, Endometrial NK cells are special immature cells that await pregnancy, *J. Immunol.* 181 (3) (2008) 1869–1876.
- [38] P. Vacca, C. Vitale, E. Montaldo, R. Conte, C. Cantoni, E. Fulcheri, V. Darretta, L. Moretta, M.C. Mingari, CD34+ hematopoietic precursors are present in human decidua and differentiate into natural killer cells upon interaction with stromal cells, *Proc. Natl. Acad. Sci. U. S. A.* 108 (6) (2011) 2402–2407.
- [39] B.A. Croy, Z. Chen, A.P. Hofmann, E.M. Lord, A.L. Sedlacek, S.A. Gerber, Imaging of vascular development in early mouse decidua and its association with leukocytes and trophoblasts, *Biol. Reprod.* 87 (5) (2012) 125.
- [40] A.A. Ashkar, J.P. Di Santo, B.A. Croy, Interferon gamma contributes to initiation of uterine vascular development, decidual integrity, and uterine natural killer cell maturation during normal murine pregnancy, *J. Exp. Med.* 192 (2) (2000) 259–270.
- [41] H. Yadi, S. Burke, Z. Madeja, M. Hemberger, A. Moffett, F. Colucci, Unique receptor repertoire in mouse uterine NK cells, *J. Immunol.* 181 (9) (2008) 6140–6147.
- [42] Z. Chen, J. Zhang, K. Hatta, P.D. Lima, H. Yadi, F. Colucci, A.T. Yamada, B.A. Croy, DBA-lectin reactivity defines mouse uterine natural killer cell subsets with biased gene expression, *Biol. Reprod.* 87 (4) (2012) 81.
- [43] C. Tayade, D. Hilchie, H. He, Y. Fang, L. Moons, P. Carmeliet, R.A. Foster, B.A. Croy, Genetic deletion of placenta growth factor in mice alters uterine NK cells, *J. Immunol.* 178 (7) (2007) 4267–4275.
- [44] M.J. Guimond, J.A. Luross, B. Wang, C. Terhorst, S. Danial, B.A. Croy, Absence of natural killer cells during murine pregnancy is associated with reproductive compromise in TgE26 mice, *Biol. Reprod.* 56 (1) (1997) 169–179.
- [45] B.A. Croy, S.D. Burke, V.F. Barrette, J. Zhang, K. Hatta, G.N. Smith, J. Bianco, A.T. Yamada, M.A. Adams, Identification of the primary outcomes that result from deficient spiral arterial modification in pregnant mice, *Pregnancy Hypertens.* 1 (1) (2011) 87–94.
- [46] M.J. Guimond, B. Wang, B.A. Croy, Engraftment of bone marrow from severe combined immunodeficient (SCID) mice reverses the reproductive deficits in natural killer cell-deficient tg epsilon26 mice, *J. Exp. Med.* 187 (2) (1998) 217–223.
- [47] A.P. Hofmann, S.A. Gerber, B.A. Croy, Uterine natural killer cells pace early development of mouse decidua basalis, *Mol. Hum. Reprod.* 20 (1) (2014) 66–76.
- [48] J.M. Monk, S. Leonard, B.A. McBey, B.A. Croy, Induction of murine spiral artery modification by recombinant human interferon-gamma, *Placenta* 26 (10) (2005) 835–838.
- [49] M.J. Soares, D. Chakraborty, M.A. Karim Rumi, T. Konno, S.J. Renaud, Rat placentation: an experimental model for investigating the hemochorial maternal-fetal interface, *Placenta* 33 (4) (2012) 233–243.
- [50] L. Vercruysse, S. Caluwaerts, C. Luyten, R. Pijnenborg, Interstitial trophoblast invasion in the decidua and mesometrial triangle during the last third of pregnancy in the rat, *Placenta* 27 (1) (2006) 22–33.
- [51] D. Chakraborty, M.A. Rumi, T. Konno, M.J. Soares, Natural killer cells direct hemochorial placentation by regulating hypoxia-inducible factor dependent trophoblast lineage decisions, *Proc. Natl. Acad. Sci. U. S. A.* 108 (39) (2011) 16295–16300.
- [52] S. Caluwaerts, L. Vercruysse, C. Luyten, R. Pijnenborg, Endovascular trophoblast invasion and associated structural changes in uterine spiral arteries of the pregnant rat, *Placenta* 26 (7) (2005) 574–584.
- [53] S. Gordon, P.R. Taylor, Monocyte and macrophage heterogeneity, *Nature reviews, Immunology* 5 (12) (2005) 953–964.
- [54] C. Auffray, D. Fogg, M. Garfa, G. Elaine, O. Join-Lambert, S. Kayal, S. Sarnacki, A. Cumano, G. Lauvau, F. Geissmann, Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior, *Science* 317 (5838) (2007) 666–670.
- [55] F. Porcheray, S. Viaud, A.C. Rimaniol, C. Léone, B. Samah, N. Dereuddre-Bosquet, D. Dormont, G. Gras, Macrophage activation switching: an asset for the resolution of inflammation, *Clin. Exp. Immunol.* 142 (3) (2005) 481–489.
- [56] J.S. Hunt, L. Miller, J.S. Platt, Hormonal regulation of uterine macrophages, *Dev. Immunol.* 6 (1–2) (1998) 105–110.
- [57] R.L. Jones, N.J. Hannan, T.J. Kaitu'u, J. Zhang, L.A. Salamonsen, Identification of chemokines important for leukocyte recruitment to the human endometrium at the times of embryo implantation and menstruation, *J. Clin. Endocrinol. Metab.* 89 (12) (2004) 6155–6167.
- [58] J.N. Bulmer, L. Morrison, J.C. Smith, Expression of class II MHC gene products by macrophages in human uteroplacental tissue, *Immunology* 63 (4) (1988) 707–714.
- [59] J.N. Bulmer, P.J. Williams, G.E. Lash, Immune cells in the placental bed, *Int. J. Dev. Biol.* 54 (2–3) (2010) 281–294.
- [60] P.J. Williams, J.N. Bulmer, R.F. Searle, B.A. Innes, S.C. Robson, Altered decidual leucocyte populations in the placental bed in pre-eclampsia and foetal growth restriction: a comparison with late normal pregnancy, *Reproduction* 138 (1) (2009) 177–184.
- [61] S.J. Renaud, C.H. Graham, The role of macrophages in utero-placental interactions during normal and pathological pregnancy, *Immunol. Invest.* 37 (5) (2008) 535–564.
- [62] S.A. Robertson, M.J. Jasper, J.J. Bromfield, A.S. Care, H. Nakamura, W.V. Ingman, The role of macrophages in implantation and early pregnancy success, *Biol. Reproduction* 78 (supplement 1) (2008) 274–275.
- [63] U. Singh, G. Nicholson, B.C. Urban, I.L. Sargent, U. Kishore, A.L. Bernal, Immunological properties of human decidual macrophages—a possible role in intrauterine immunity, *Reproduction* 129 (5) (2005) 631–637.
- [64] S. Engert, L. Rieger, M. Kapp, J.C. Becker, J. Dietl, U. Kämmerer, Profiling chemokines, cytokines and growth factors in human early pregnancy decidua by protein array, *Am. J. Reprod. Immunol.* 58 (2) (2007) 129–137.
- [65] C. Gustafsson, J. Mjösberg, A. Matussek, R. Geffers, L. Matthiesen, G. Berg, S. Sharma, J. Buer, J. Ernerudh, Gene expression profiling of human decidual macrophages: evidence for immunosuppressive phenotype, *PloS One* 3 (4) (2008) e2078.
- [66] M. Piacentini, F. Autuori, Immunohistochemical localization of tissue transglutaminase and Bcl-2 in rat uterine tissues during embryo implantation and post-partum involution, *Differentiation* 57 (1) (1994) 51–61.
- [67] V.M. Abrahams, Y.M. Kim, S.L. Straszewski, R. Romero, G. Mor, Macrophages and apoptotic cell clearance during pregnancy, *Am. J. Reprod. Immunol.* 51 (4) (2004) 275–282.
- [68] U. Kämmerer, A.O. Eggert, M. Kapp, A.D. McLellan, T.B. Geijtenbeek, J. Dietl, Y. van Kooyk, E. Kämpgen, Unique appearance of proliferating antigen-presenting cells expressing DC-SIGN (CD209) in the decidua of early human pregnancy, *Am. J. pathology* 162 (3) (2003) 887–896.
- [69] G. Laskarin, K. Cupurdija, V.S. Tokmadzic, D. Dorcic, J. Dupor, K. Juretic, N. Strbo, T.B. Crncic, F. Marchezi, P. Allavena, A. Mantovani, L. Randic, D. Rukavina, The presence of functional mannose receptor on macrophages at the maternal-fetal interface, *Hum. Reprod.* 20 (4) (2005) 1057–1066.
- [70] J. Svensson, M.C. Jenmalm, A. Matussek, R. Geffers, G. Berg, J. Ernerudh, Macrophages at the fetal-maternal interface express markers of alternative activation and are induced by M-CSF and IL-10, *J. Immunol.* 187 (7) (2011) 3671–3682.
- [71] B.L. Houser, T. Tilburgs, J. Hill, M.L. Nicotra, J.L. Strominger, Two unique human decidual macrophage populations, *J. Immunol.* 186 (4) (2011) 2633–2642.
- [72] D. Schonkeren, M.L. van der Hoorn, P. Khedoe, G. Swings, E. van Beelen, F. Claas, C. van Kooten, E. de Heer, S. Scherjon, Differential distribution and phenotype of decidual macrophages in preclimptic versus control pregnancies, *Am. J. pathology* 178 (2) (2011) 709–717.
- [73] E. Gomez Perdiguerro, K. Klaproth, C. Schulz, K. Busch, E. Azzoni, L. Crozet, H. Garner, C. Trouillet, M.F. de Bruijn, F. Geissmann, H.R. Rodewald, Tissue-resident macrophages originate from yolk-sac-derived erythro-myeloid progenitors, *Nature* 518 (7540) (2015) 547–551.
- [74] P. Italiani, D. Boraschi, From monocytes to M1/M2 macrophages: phenotypic vs. Functional differentiation, *Front. Immunol.* 5 (2014) 514.
- [75] K. Kierdorf, M. Prinz, F. Geissmann, E. Gomez Perdiguerro, Development and function of tissue resident macrophages in mice, *Seminars Immunol.* 27 (6) (2015) 369–378.
- [76] L. Ziegler-Heitbrock, P. Ancuta, S. Crowe, M. Dalod, V. Grau, D.N. Hart, P.J. Leenen, Y.J. Liu, G. MacPherson, G.J. Randolph, J. Scherberich, J. Schmitz, K. Shortman, S. Sozzani, H. Strobl, M. Zembala, J.M. Austyn, M.B. Lutz, Nomenclature of monocytes and dendritic cells in blood, *Blood* 116 (16) (2010) e74–e80.
- [77] B.N. Melgert, F. Spaans, T. Borghuis, P.A. Klok, B. Groen, A. Bolt, P. de Vos, M.G. van Pampus, T.Y. Wong, H. van Goor, W.W. Bakker, M.M. Faas, Pregnancy and preeclampsia affect monocyte subsets in humans and rats, *PloS One* 7 (9) (2012) e45229.
- [78] B. Groen, A.E. van der Wijk, P.P. van den Berg, J.D. Lefrandt, G. van den Berg, K.M. Sollie, P. de Vos, T.P. Links, M.M. Faas, Immunological adaptations to pregnancy in women with type 1 diabetes, *Sci. Rep.* 5 (2015) 13618.
- [79] L. Ziegler-Heitbrock, Blood monocytes and their subsets: established features and open questions, *Front. Immunol.* 6 (2015) 423.
- [80] E. Tagliani, C. Shi, P. Nancy, C.S. Tay, E.G. Pamer, A. Erlebacher, Coordinate regulation of tissue macrophage and dendritic cell population dynamics by CSF-1, *J. Exp. Med.* 208 (9) (2011) 1901–1916.
- [81] J. Yang, L. Zhang, C. Yu, X.F. Yang, H. Wang, Monocyte and macrophage differentiation: circulation inflammatory monocyte as biomarker for inflammatory diseases, *Biomark. Res.* 2 (1) (2014) 1.
- [82] Y. Xu, R. Romero, D. Miller, L. Kadam, T.N. Mial, O. Plazyo, V. Garcia-Flores, S.S. Hassan, Z. Xu, A.L. Tarca, S. Drewilo, N. Gomez-Lopez, An M1-like macrophage polarization in decidual tissue during spontaneous preterm labor that is attenuated by rosiglitazone treatment, *J. Immunol.* 196 (6) (2016) 2476–2491.
- [83] N.C. Douglas, R.C. Zimmermann, Q.K. Tan, C.S. Sullivan-Pyke, M.V. Sauter, J.K. Kitajewski, C.J. Shawber, VEGFR-1 blockade disrupts peri-implantation

- decidual angiogenesis and macrophage recruitment, *Vasc. Cell* 6 (2014) 16.
- [84] O. Shynlova, T. Nedd-Roderique, Y. Li, A. Dorogin, T. Nguyen, S.J. Lye, Infiltration of myeloid cells into decidua is a critical early event in the labour cascade and post-partum uterine remodelling, *J. Cell Mol. Med.* 17 (2) (2013) 311–324.
- [85] D.R. Tessier, S. Raha, A.C. Holloway, J. Yockell-Lelievre, C. Tayade, A. Gruslin, Characterization of immune cells and cytokine localization in the rat uteroplacental unit mid- to late gestation, *J. Reprod. Immunol.* 110 (2015) 89–101.
- [86] C. Ferretti, L. Bruni, V. Dangles-Marie, A.P. Pecking, D. Bellet, Molecular circuits shared by placental and cancer cells, and their implications in the proliferative, invasive and migratory capacities of trophoblasts, *Hum. Reprod. update* 13 (2) (2007) 121–141.
- [87] F. Garrido, F. Ruiz-Cabello, N. Aptsiauri, Rejection versus escape: the tumor MHC dilemma, *Cancer Immunol. Immunother.* CII 66 (2) (2017) 259–271.
- [88] E.M. Levy, M.P. Roberti, J. Mordoh, Natural killer cells in human cancer: from biological functions to clinical applications, *J. Biomed. Biotechnol.* 2011 (2011) 676198.
- [89] N.B. Hao, M.H. Lu, Y.H. Fan, Y.L. Cao, Z.R. Zhang, S.M. Yang, Macrophages in tumor microenvironments and the progression of tumors, *Clin. Dev. Immunol.* 2012 (2012) 948098.
- [90] M. Gulubova, I. Manolova, D. Kyurkchiev, A. Julianov, I. Altunkova, Decrease in intrahepatic CD56+ lymphocytes in gastric and colorectal cancer patients with liver metastases, *APMIS* 117 (12) (2009) 870–879.
- [91] P. Carrega, B. Morandi, R. Costa, G. Frumento, G. Forte, G. Altavilla, G.B. Ratto, M.C. Mingari, L. Moretta, G. Ferlazzo, Natural killer cells infiltrating human nonsmall-cell lung cancer are enriched in CD56 bright CD16(–) cells and display an impaired capability to kill tumor cells, *Cancer* 112 (4) (2008) 863–875.
- [92] M. Carlsten, H. Norell, Y.T. Bryceson, I. Poschke, K. Schedvins, H.G. Ljunggren, R. Kiessling, K.J. Malmberg, Primary human tumor cells expressing CD155 impair tumor targeting by down-regulating DNAM-1 on NK cells, *J. Immunol.* 183 (8) (2009) 4921–4930.
- [93] F. Katou, H. Ohtani, Y. Watanabe, T. Nakayama, O. Yoshie, K. Hashimoto, Differing phenotypes between intraepithelial and stromal lymphocytes in early-stage tongue cancer, *Cancer Res.* 67 (23) (2007) 11195–11201.
- [94] T. Baessler, J.E. Charton, B.J. Schmiedel, F. Grunebach, M. Krusch, A. Wacker, H.G. Rammensee, H.R. Salih, CD137 ligand mediates opposite effects in human and mouse NK cells and impairs NK-cell reactivity against human acute myeloid leukemia cells, *Blood* 115 (15) (2010) 3058–3069.
- [95] B.Z. Qian, J.W. Pollard, Macrophage diversity enhances tumor progression and metastasis, *Cell* 141 (1) (2010) 39–51.
- [96] L. Bingle, N.J. Brown, C.E. Lewis, The role of tumour-associated macrophages in tumour progression: implications for new anticancer therapies, *J. pathology* 196 (3) (2002) 254–265.
- [97] D.G. DeNardo, D.J. Brennan, E. Rexhepaj, B. Ruffell, S.L. Shiao, S.F. Madden, W.M. Gallagher, N. Wadhvani, S.D. Keil, S.A. Junaid, H.S. Rugo, E.S. Hwang, K. Jirstrom, B.L. West, L.M. Coussens, Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy, *Cancer Discov.* 1 (1) (2011) 54–67.
- [98] C. Steidl, T. Lee, S.P. Shah, P. Farinha, G. Han, T. Nayar, A. Delaney, S.J. Jones, J. Iqbal, D.D. Weisenburger, M.A. Bast, A. Rosenwald, H.K. Muller-Hermelink, L.M. Rimsza, E. Campo, J. Delabie, R.M. Braziel, J.R. Cook, R.R. Tubbs, E.S. Jaffe, G. Lenz, J.M. Connors, L.M. Staudt, W.C. Chan, R.D. Gascoyne, Tumor-associated macrophages and survival in classic Hodgkin's lymphoma, *N. Engl. J. Med.* 362 (10) (2010) 875–885.
- [99] C. Murdoch, A. Giannoudis, C.E. Lewis, Mechanisms regulating the recruitment of macrophages into hypoxic areas of tumors and other ischemic tissues, *Blood* 104 (8) (2004) 2224–2234.
- [100] S.M. Ong, Y.C. Tan, O. Beretta, D. Jiang, W.H. Yeap, J.J. Tai, W.C. Wong, H. Yang, H. Schwarz, K.H. Lim, P.K. Koh, K.L. Ling, S.C. Wong, Macrophages in human colorectal cancer are pro-inflammatory and prime T cells towards an anti-tumour type-1 inflammatory response, *Eur. J. Immunol.* 42 (1) (2012) 89–100.
- [101] P. Dumont, A. Berton, N. Nagy, F. Sandras, S. Tinton, P. Demetter, F. Mascart, A. Allaoui, C. Decaestecker, I. Salmon, Expression of galectin-3 in the tumor immune response in colon cancer, *Lab. Invest.* 88 (8) (2008) 896–906.
- [102] S.K. Biswas, L. Gangi, S. Paul, T. Schioppa, A. Saccani, M. Sironi, B. Bottazzi, A. Doni, B. Vincenzo, F. Pasqualini, L. Vago, M. Nebuloni, A. Mantovani, A. Sica, A distinct and unique transcriptional program expressed by tumor-associated macrophages (defective NF-kappaB and enhanced IRF-3/STAT1 activation), *Blood* 107 (5) (2006) 2112–2122.
- [103] A. Mantovani, A. Sica, P. Allavena, C. Garlanda, M. Locati, Tumor-associated macrophages and the related myeloid-derived suppressor cells as a paradigm of the diversity of macrophage activation, *Hum. Immunol.* 70 (5) (2009) 325–330.
- [104] A. Mantovani, S. Sozzani, M. Locati, P. Allavena, A. Sica, Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes, *Trends Immunol.* 23 (11) (2002) 549–555.
- [105] K. Fukuda, A. Kobayashi, K. Watabe, The role of tumor-associated macrophage in tumor progression, *Front. Biosci.* 4 (2012) 787–798.
- [106] S.F. Schoppmann, P. Birner, J. Stockl, R. Kalt, R. Ullrich, C. Caucig, E. Kriehuber, K. Nagy, K. Alitalo, D. Kerjaschki, Tumor-associated macrophages express lymphatic endothelial growth factors and are related to peritumoral lymphangiogenesis, *Am. J. pathology* 161 (3) (2002) 947–956.
- [107] C. Guruvayoorappan, Tumor versus tumor-associated macrophages: how hot is the link? *Integr. cancer Ther.* 7 (2) (2008) 90–95.
- [108] P.J. Polverini, S.J. Leibovich, Effect of macrophage depletion on growth and neovascularization of hamster buccal pouch carcinomas, *J. oral pathology* 16 (9) (1987) 436–441.
- [109] A. Ben-Baruch, Inflammation-associated immune suppression in cancer: the roles played by cytokines, chemokines and additional mediators, *Seminars cancer Biol.* 16 (1) (2006) 38–52.